The Incidence of acute Neurotoxicity among some Iraqi colorectal cancer patients treated with oxaliplatin-based chemotherapy

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Abstract:

Oxaliplatin serves as the primary treatment option for colorectal cancer (CRC) at all stages. It induces acute cold-triggered neurotoxicity and chronic cumulative neurotoxicity, leading to potential dose adjustments and influencing patient quality of life (QOL). However, conventional strategies are lacking for effectively managing oxaliplatin-induced neurotoxicity (OIN).

This observational study is a prospective aimed at investigating the incidence and associated factors of OIN involving 120 patients with CRC at different stages under oxaliplatin-based chemotherapy. The demographic and clinical characteristics of the patients were collected using a preformed data information sheet. The frequency and associated factors were evaluated after the third cycle of the Oxaliplatin chemotherapy. Unfortunately, 84 patients (70%) developed neurotoxicity while 30% did not experience this side effect. None of the included demographic or clinical characteristics were significantly associated with the OIN. Thus, it did not appear to predict neurotoxicity risk in the studied population. Other factors such as genetics could have such an impact and need to be investigated.

Keywords: Colorectal cancer, Oxaliplatin, neurotoxicity, risk factors

تكرار التهاب الأعصاب الحاد لدى بعض المرضى العراقيين المصابين بسرطان القولون والمستقيم الذين يخضعون للعلاج الكيميائي المعتمد على أوكساليبلاتين

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خلاصة

يعتبر أوكساليبلاتين بمثابة خيار العلاج الأساسي لسرطان القولون والمستقيم. ولكنه يحفز السمية العصبية الحادة الناجمة عن التعرض للاشياء الباردة والاعتلال العصبي التراكمي المزمن، مما يؤدي إلى تعديلات في الجرعة المحتملة والتأثير على نوعية حياة المريض. هدفت الدراسة الى تحديد العوامل الديموغرافية والسريرية لتطور سمية الأعصاب الناجمه عن استعمال علاج

الأوكساليبلاتين. هذه الدراسة الملاحظة هي مستقبلية تهدف إلى التحقيق من مدى تاثير العوامل المرتبطة بالتهاب الأعصاب الناجم عن أوكساليبلاتين شملت 120 مريضًا مصابًا بسرطانات القولون والمستقيم. تم جمع الخصائص الديموغرافية والسريرية للمرضى في ورقة معلومات البيانات المعدة مسبقا. تم تقييم التكرار والعوامل المرتبطة بالسمية العصبية بعد الدورة الثالثة من العلاج.لسوء الحظ أظهرت النتائج ان 84 مريضًا (70٪) اصيب بالسمية العصبية بينما لم يعاني 30٪ من هذا التأثير الجانبي. لم تظهر أي من الخصائص الديموغرافية والسريرية المتضمنة وجود ارتباط معنوي مع السمية العصبية وبالتالي، لا يمكن أن يتنبأ بمخاطر السمية العصبية لدى المرضى الذين شملتهم الدراسة. يمكن لعوامل أخرى مثل العوامل الوراثية الجينية أن يكون لها مثل هذا التأثير وتحتاج إلى دراسات مستقبلية.

الكلمات المفتاحية: سرطان القولون والمستقيم، أوكساليبلاتين، السمية العصبية، عوامل الخطر

Introduction

Colorectal cancer (CRC) is a significant health issue in the world with a high mortality rate[1,2]. Colorectal cancer is the third most commonly diagnosed and the second most fatal cancer worldwide[3]. This tumor usually develops in people over the age of 50 but in recent years it has been shown that there is an increase in the incidence of colorectal cancer at a young age[4]. In the previous study by Ibrahim S, et.al on trends in colorectal cancer in Iraq over two decades showed rising incidence and mortality of CRC in all age groups[5].

Oxaliplatin is the most common first-line chemotherapeutic agent for patients with all stages of colorectal cancer[6]. Oxaliplatin has central and peripheral neurotoxicity. It elicits a dislocation of the Zonula Occludens-1 (ZO-1), one of the tight junction proteins that make contributions to constituting the blood-brain barrier. The extended permeability of the blood-brain barrier permits the chemotherapy agent to enter the mind parenchyma, affecting both the neuronal and glial cubicles, and can set off cognitive impairment and impairment of verbal reminiscence (7). Oxaliplatin can cause acute cold-induced neurotoxicity and chronic cumulative neurotoxicity, requiring dose modification and impacting the quality of life (QOL)(8). Early identification of neurotoxicity and changes in dosage or dosing schedule could prevent chronic symptoms, which, once established, may take many months or years to resolve, or may even persist throughout life with substantial detrimental effects on QOL(9).

Acute neurotoxicity may occur and is indicated by paresthesia (skin sensations of burning or tingling), dysesthesia (altered skin sensations accompanied with pain), or both symptoms and typically, this condition improves within hours or days. This is indicated by data obtained in research, particularly where the dosage range is 130-180 mg/m^2(10). Sometimes, temporarily, in 1% to 2% of the patients, there may be dysesthesia of the pharyngolaryngeal area, leading to dyspnea or dysphagia(11). The degree and speed of infusion define this acute syndrome according to the research. Doubling the infusion time for the second and other therapies prevents recurrence(12)… This is because the mean C^{max} is reduced by approximately 32% when the infusion time is increased from 2 to more than 6 hours(13). The other manifestation observed in association with the acute syndrome is muscle contraction. Some people refer to them as “spasms” or “cramps,” hand or feet rigidity or inability to let go of an object, sometimes it includes the legs or jaw. Vulnerable nerves are also weakened or worsened if they come into contact with cold. describing the Lhermitte sign which is an electrical shock-like sensation running down the back and sometimes into the limb which

indicates a lesion involving dorsal column nuclei of the medulla very few cases have been reported in patients using oxaliplatin(14). Motor neurotoxicity symptoms manifest as muscle weakness, fasciculations, prolonged muscle contractions, and muscle atrophy leading to postural instability, compromised mobility, and increased morbidity (15). These symptoms typically exhibit a symmetrical and distal progression, initiating with weakness in the toes and advancing to the ankle and knee regions (16).

Various studies have analyzed predictors for oxaliplatin-induced neurotoxicity (17–19). Nevertheless, effective strategies for managing neurotoxicity in affected patients remain elusive. Thus, in addition to improving QOL for chemotherapy patients, the need for methods to better identify patients at risk of neurotoxicity remains unmet. This prospective study was undertaken to identify predictors of neurotoxicity development to help guide future strategies toward improving safety, efficacy, and QOL among some Iraqi patients treated with oxaliplatin.

Patients and methods

Patients

This study prospectively analyzed 120 cancer patients who received oxaliplatin at two centers Warth International Foundation for Oncology Treatment in Karbala and at Oncology Teaching Hospital at Medical City-Baghdad under the supervision of oncologists and National Comprehensive Network (NCCN) dependent guidelines, between December 2023 and June 2024. All procedures were performed according to the ethical standards of the Ethics Review Committee at Mustansiriyha University of Pharmacy (approval no. 37) and the approval of the Ministry of Health no. 7026. Given the prospective nature of this work, the need to obtain informed consent was waived for the individual participants included in the study. This was done by the ethics review committee at the Ministry of Health. The written informed consent indicated that all collected data will be used for research purposes only; and that the information will be kept secret from all except the research investigators. Participants were informed that enrolment in the study will be voluntary that they have the right not to take part in the study without penalty and that the anonymity and confidentiality of the information will be ensured by using a code number for each participant instead of their name or file number.

Inclusion and Exclusion Criteria

Patients with colorectal adenocarcinoma primary tumors receiving oxaliplatin-based regimens were eligible for the study. Patients with anemia, hypomagnesemia, and neuropathy, and those unable to provide appropriate data were excluded from the study.

Demographic and clinical data

Patients were interviewed to collect demographic data and medical history using a data collection sheet. Patients were asked to answer all items including demographic data (age, sex, height, and weight calculated (body surface area and body mass index [BMI]), residence, smoking status, family history of colorectal cancer, education level, patient performance state according to ECOG score). ECOG score patients with a better performance status (ECOG 0-2) are typically considered to have a better prognosis and may be candidates for more aggressive treatment options. Patients with a poorer performance status (ECOG 3-5) may have a worse prognosis and may require more supportive care (20).

Clinical data include presenting symptoms, primary tumor site, tumor stage, organs involved in distant metastasis, date of diagnosis, comorbidities, and serum level of Carcino Embryonic Antigen (CEA) at diagnosis.

Treatment-related data include chemotherapy setting and date, chemotherapy regimen (FOLFOX: 5-fluorouracil, oxaliplatin (85 mg/m2) and leucovorin; XELOX: capecitabine plus oxaliplatin (130 mg/m2) with or without bevacizumab; the number of cycles, concomitant medications (Valsartan with amlodipine, Glucophage, statin, any vitamins or supplements), total cumulative dose, deviation from standard dose and company manufacturer of oxaliplatin.

Concomitant medication was defined as the administration of another drug for 2 weeks at the time of evaluation.

In every chemotherapy cycle, data was collected according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE; version 5). The patients were followed up for at least three cycles of oxaliplatin-based chemotherapy.

Statistical analysis

Statistical analyses were performed using SPSS software version 25.0 (SPSS, Chicago). Continuous data were subjected to a normality test (Shapiro Wilk test), Data with normal distribution were presented as mean and standard deviation, and analyzed with a student t-test. Data with non-normal distribution were presented as median and range and analyzed with the Mann-Whitney U test. Categorical variables were expressed as numbers and percentages and analyzed with a Chi-square test. A p-value less than 0.05 was considered to indicate a statistically significant difference.

Results

Incidence of acute neurotoxicity

After completion of the third cycle of chemotherapy, 84 patients (70%) developed neurotoxicity while 36 patients (30%) had no neurotoxicity (figure 1).

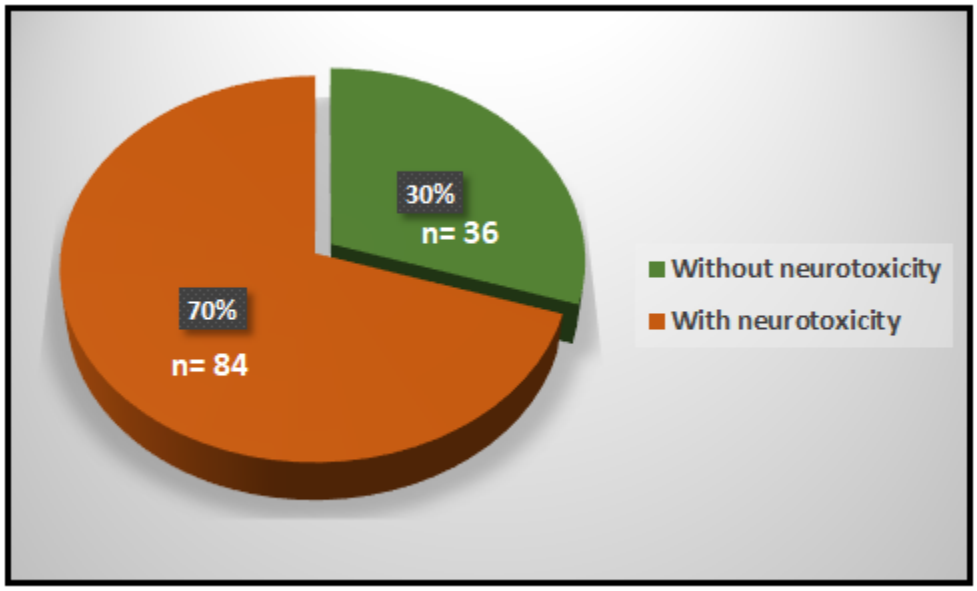

Figure 1: Incidence of neurotoxicity in patients with CRC under oxaliplatin-based therapy after the third cycle.

Demographic and clinical characteristics of the patients

Demographic and clinical data of the participants with the potential variables related to the development of OIN are illustrated in Tables 1 and 2.

The variables of demographic data in Table 1 (Age, disease duration, sex, body mass index, educational level, residence, family history of CRC, smoking, and ECOG (Eastern Cooperative Oncology Group) performance status) did not show significant differences in association with OIN.

Table 1 Association of demographic characteristics with the risk of acute neurotoxicity

Variables	Without neurotoxicity (n=36)	With neurotoxicity (n= 84)	p-value
Age, years Mean±SD Range	 52.89±10.68 20-71	 53.48±13.18 18-77	0.814
Disease duration, months Mean±SD Range	 6.94±5.71 0.5-12	 8.25±6.43 0.2-12	0.133
Sex Male Female	 17(47.22%) 19(52.78%)	 39(46.43%) 45(53.57%)	0.936
Body mass index, kg/m^2 Mean±SD Range	 27.53±5.78 15.9-41	 28.25±6.46 15.92-49.6	0.568
Educational level Primary Secondary Higher	 25(69.44%) 4(11.11%) 7(19.44%)	 50(59.52%) 19(22.62%) 15(17.86%)	0.337
Residence Baghdad North governorates South governorates	 26(72.22%) 4(11.11%) 6(16.67%)	 51(60.71%) 8(9.52%) 25(29.76%)	0.324
Family history of CRC No Yes	 30(83.33%) 6(16.67%)	 67(79.76%) 17(20.24%)	0.649
Smoking Never Ex/current	 31(86.11%) 5(13.89%)	 63(75%) 21(25%)	0.176
ECOG 0 1 2	 27(75%) 8(22.22%) 1(2.78%)	 68(80.95%) 16(19.05%) 0(0%)	0.276

(ECOG) Eastern Cooperative Oncology Group, CRC colorectal cancer

The variables of clinical data in Table 2 such as past medical history, concomitant medications, primary tumor site, metastasis, tumor stage, CEA levels, chemotherapy settings, different treatment protocols, company, the dose of Oxaliplatin per body surface area (BSA) and response rates also did not show significant differences between individuals with or without neurotoxicity.

Table 2: Association of clinical characteristics with acute neurotoxicity.

Variables	Without neurotoxicity (n=36)	With neurotoxicity (n= 84)	p-value
Past medical history			
None	24(66.67%)	58(69.05%)	0.797
HTN	6(16.67%)	19(22.62%)	0.462
DM	5(13.89%)	10(11.9%)	0.763
Others	1(2.78%)	3(3.57%)	0.824
Concomitant medications			
Valsartan +amlodipine	6(16.67%)	23(27.38%)	0.236
Statin	10(27.78%)	19(22.62%)	0.545
Metformin	4(11.11%)	10(11.9%)	0.690
Primary tumor site			
Colon	16(44.44%)	30(35.71%)	
Recto-sigmoid	8(22.22%)	17(20.24%)	0.737
Rectum	8(22.22%)	24(28.57%)	
Sigmoid	4(11.11%)	13(15.48%)	
Metastasis			
No metastasis	17(47.22%)	37(44.05%)	
Liver	13(36.11%)	27(32.14%)	0.194
Liver and lung	1(2.78%)	9(10.71%)	
>3 organs	4(11.11%)	3(3.57%)	
Others	1(2.78%)	8(9.52%)	
Tumor stage			
II	3(8.33%)	6(7.14%)	
III	12(33.33%)	30(35.71%)	0.954
IV	21(58.33%)	48(57.14%)	
CEA			
Median	18.88	6.75	0.559
Range	0.3-1500	0.2-2000	
Chemotherapy settings			
Neoadjuvant	16(44.44%)	39(44.43%)	
Palliative	16(44.44%)	37(44.05%)	0.707
Adjuvant	2(5.56%)	10(11.9%)	
Company			
X	13(36.11%)	34(40.48%)	0.635
Y	23(63.89%)	50(59.52%)	
Protocol			
Xelox	13(36.11%)	33(39.29%)	0.896
Xelox+avastin	12(33.33%)	24(28.57%)	
Folfox	3(8.33%)	10(11.9%)	

Folfox+avastin	8(22.22%)	17(20.24%)	
Dose of oxaliplatin, mg/BSA Mean±SD Range	 193.1±41.52 100-270	 181.56±46.6 100-260	 0.204
Response Complete response Partial response Stable disease Progressive disease Lost follow up	 2(5.56%) 19(52.78%) 5(13.89%) 10(27.78%) 0(0%)	 3(3.57%) 45(53.57%) 9(10.71%) 22(26.19%) 5(5.81%)	 0.622

HTN : hypertension, DM : diabetes mellites, CEA Carcino Embryonic Antigen

Discussion

The study provides insights into neurotoxicity distribution among Some Colorectal cancer patients. It presents data on the distribution of neurotoxicity occurrence. It indicates that 70% of patients developed neurotoxicity while 30% did not experience this side effect after the third cycle of chemotherapy.

Although there is no significant difference between residents, Baghdad, North governorates, and South governorates, the South governorates have a higher percentage of neurotoxicity patients (29.76%) than (16.67%) with no neurotoxicity development. This may be due to differences in physique and BMI between the South governorates' and North governorates' populations. In some studies, BMI was identified as a significant predictor of the development of OIN, and obesity was reported as a risk factor for chemotherapy-induced peripheral neurotoxicity (21,22). In addition, when body fat content is high, anticancer drugs accumulate in adipose tissue, and they are not excreted as soon as they are necessary. Clinicians should pay close attention to the onset of OIN among patients with high BMI, and not necessarily just the obese population. Our results only suggest that the more patients in southern governorates have a higher BMI, the more likely OIN is to occur. Further investigation of these issues in different populations is warranted.

Although smoking has been linked to an increased risk of neurotoxicity in our study the difference in p-value is not significant (0.176), but the percent of patients who developed neurotoxicity is (25%) compared with patients who did not develop neurotoxicity (13.89%) means the result is consistent with previous studies that suggest smoking can induce changes in DNA methylation patterns and histone modifications, leading to the dysregulation of pro-nociceptive and anti-nociceptive genes in sensory nerves and neurons after nerve injury, contributing to chronic pain development(23,24). These epigenetic alterations may affect key ion channels and neurotransmitter receptors in the dorsal root ganglion, influencing synaptic plasticity in the spinal cord and exacerbating neurotoxic pain symptoms. Additionally, nicotine addiction and smoking have been identified as risk factors for neuropathic pain. The duration of smoking and addiction levels positively correlate to the likelihood of experiencing neuropathic pain, especially in individuals with diabetes(25).

Although concomitant use of angiotensin receptor antagonist was not extracted as a significant variable, in a previous study the combined use of valsartan angiotensin receptor antagonist tended to reduce OIN(18). In contrast, the concomitant use of

amlodipine was suggested to represent a risk factor for OIN. Amlodipine, a commonly prescribed antihypertensive drug metabolized by CYP3A4, can cause various side effects and drug interactions. Amlodipine has several side effects, including peripheral neuropathy, weight loss, delayed nerve conduction, and transient neurotoxicity(26). Therefore, hypertensive patients on (valsartan and amlodipine) have neurotoxicity (27.38%) while those without neurotoxicity (16.67%). Further research is needed and clinicians should also be careful about prescribing amlodipine when chemotherapy with oxaliplatin. Therefore, valsartan could not prevent OIN due to its combination with amlodipine.

Diabetic patients with type II in this study (13.89%) were without neurotoxicity and (11.9%) with neurotoxicity. Although some studies demonstrated that diabetes is considered a risk factor for developing OIN the relationship between oxaliplatin-induced neurotoxicity and diabetes is not established(27,28). That diabetic patients enrolled in this study, were treated with metformin, which is considered an antioxidant that contributes to protective factors.

Patients who take statins in this study had no significant effect on neurotoxicity (22.62%), while those without neurotoxicity (27.78%). One proposed mechanism of statins in boosting the antioxidant system is through their ability to upregulate the expression of antioxidant enzymes, such as superoxide dismutase and catalase. These enzymes play a crucial role in neutralizing reactive oxygen species, which are known to contribute to oxidative stress and tissue damage. By enhancing the antioxidant defense system, statins may help protect against neurotoxicity and other oxidative stress-related conditions(29,30).

The use of adjuvant protocols in colorectal cancer treatment in our study does not significantly impact the risk of neurotoxicity when compared with other chemotherapy settings. However, the percentage of patients who use adjuvant protocols and develop neurotoxicity is (11.9%) and those who have not developed neurotoxicity is (5.56%). It is consistent with another study suggesting adjuvant cancer treatment protocols can increase neurotoxicity risk(31).

Because of the dosing modifications of oxaliplatin, the neurotoxicity risk was reduced in the Current study. There is no significant difference between patients that developed neurotoxicity and those that were not. Although higher Mean±SD in a patient without neurotoxicity (193.1±41.52) compared with a patient that acquired neurotoxicity (181.56±46.6) this indicates the presence of some protective factor that reduces the risk of developing neurotoxicity like the use of statins or metformin that boosts the antioxidant system in the body. Further investigation into these issues is needed.

Although there is no significant difference between chemotherapy regimens [FOLFOX: 5-fluorouracil, oxaliplatin (85 mg/m²) and leucovorin; XELOX: capecitabine plus oxaliplatin (130 mg/m²) with or without bevacizumab that developed neurotoxicity and those that are not developing neurotoxicity. Xelox protocol had the highest percentage of the population that had neurotoxicity (39.29%) compared to other protocols. This may be due to the dose of oxaliplatin (130 mg/m²) in the XELOX protocol being more than that in the FOLFOX protocol (85 mg/m2) as well as the presence of bevacizumab reducing the risk of neurotoxicity. This result is inconsistent with other studies that highlighted that bevacizumab can lead to oxaliplatin-induced neurotoxicity in stage four colorectal patients

and may increase the risk of neuro complications(32,33).

Accordingly, there appears to be no significant relationship between chemotherapy responses and neurotoxicity, suggesting that other factors may influence neurotoxicity development in addition to treatment efficacy. It is possible that individual patient characteristics, such as genetic predisposition, contribute to neurotoxicity. Further research is needed to better understand the complex relationship between chemotherapy responses and neurotoxicity This will improve patient outcomes and minimize treatment-related side effects.

Limitations to the current study need to be considered. First, confounding, selection, and information biases cannot be fully excluded from this study. That is, full information about the participants (e.g., general information regarding behaviors and psychological state, financial status of living and social interactions, seasonal changes). Other factors that may affect human health positively or negatively are genetic and epigenetic.

In conclusion

Demographic and clinical data were identified as nonsignificant risk factors for the development of oxaliplatin-induced neuropathy. The current findings represent a comprehensive statistical analysis of the incidence of neurotoxicity, shedding light on various aspects related to its development. This quantitative analysis of the data provides valuable insights that may assist in developing strategies to improve the quality of life among patients receiving oxaliplatin. However, these findings need to be confirmed in further studies to ensure their reliability and generalizability.

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Conflicts of Interest

The authors declare no conflict of interest.

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